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SEARCH

troglitazone

Company

Indications

Ddb Aleतs Drug

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Actions

Patents Meetings Companies

Personal

Highest Dev Status

Withdrawn

Sankyo Co

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Related information

Diabetes mellitus Non-insulin dependent diabetes

insulin sensitizer

Hypoglycemic agent PPAR agonist 5-HETE modulator

Reason for update on 09 June 2004

1 reference added [542814]

rowse indexes

arch Center

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O COMPANY O NEWS O ADD TO LIBRARY Actions REFERENCES FIND SIMILAR PRINT VIEW DEMAIL IF UPDATED D PATENT WORD VIEW

Summary

company decided, following discussions with the FDA, that it was in the best interests of patients to data, reported in April 2000, described **troglitazone** as having potential as an anticancer agent in head and dependent diabetes (NIDDM) [237320] but has since been withdrawn from these markets. Some preclinical Traglitazone, a peroxisome proliferator activated receptor (PPAR) agonist, was launched by Sankyo in In March 2000, Warner-Lambert voluntarily discontinued the sale of troglitazone from the US market. The neck squamous cell carcinoma [362460]. Japan in April 1997, and in the US by Parke-Davis in March 1997 [270683] for the treatment of non-insulin

of trogiltazone [360696]. Sankyo also voluntarily discontinued the sale of trogiltazone in both Japan and into allegations that Warner-Lambert had manipulated adverse-event reports regarding the toxic liver effects discontinue marketing troglitazone at that time [360409]. The FDA subsequently opened an investigation the US [363389]. By January 2003, the FDA had withdrawn its approval [476981].

In April 2000, class action lawsuits against Warner-Lambert and Parke-Davis were filed in the US District Court for the District of New Jersey and in the federal court in Philadelphia. The suits allege that the alleges that the defendant's product warnings were wholly inadequate and failed to warn prescribing physicians and patients of the actual heart and liver risks associated with the compound [362272] defendants misled potential users of troglitazone concerning the health risks associated with the drug and

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Results Summary > Drug Report

IDdb Portal Ddb Alerts ersonal Drug earch Center rowse Indexes owse Database SEARCH Indications Company pioglitazone Highest Dev Status Technologies

Actions

Launched Takeda Pharmaceutical Co Ltd

Hyperlipidemia

Cerebrovascular ischemia Hypertension Myocardial Infarction Atherosclerosis Non-insulin dependent diabetes

Antihypercholesterolemic agent Tablet formulation

PPAR gamma agonist

insulin sensitizer

Hypoglycemic agent

O COMPANY Related information REFERENCES O WORD VIEW PRINT VIEW 🗘 ADD TO LIBRARY ENAIL IF UPDATED Actions DPATENT O FIND SIMILAR NEWS

Minor editorial amendment

Reason for update on 23 February 2006

Summary

phase III trials for atherosclerosis [491975]; these trials were ongoing in March 2005 [606970] expanded to include more than 70 countries within Europe, the Middle East, Africa and Asia Pacific in August type 2 diabetes) [181756]. Takeda was initially copromoting the drug in the US with Eli Lilly, and this was been launched extensively by Takeda for the treatment of non-insulin dependent diabetes mellitus (NIDDM) Pioglitazone is a peroxisome proliferator-activated receptor (PPAR)-gamma agonist, which, by late 2000, had hypertension were published [570792], [570772]. [515419]. In November 2004, clinical data showing the efficacy of the drug for the treatment of hypertension and for the potential prevention of myocardial infarction and stroke. In May 2003, it was in 1999 [**338000**]. The company is also developing the drug for the potential treatment of atherosclerosis,

ATHEROSCLEROSIS

In November 2004, clinical data demonstrating the relative efficacy of ploglitazone (30 mg/day) compared to rosiglitazone (4 mg/day) on blood lipids and insulin sensitivity were presented at the AHA meeting in New Orleans, LA. Results from the randomized, double-blind, multicenter trial in 735 patients with type 2 diabetes showed that both drugs exhibited similar degrees of glycemic control. However, at week 24

2006/03/06

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rosiglitazone

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SmithKline Beecham plc

Launched

Psoriasis Alzheimers disease

Asthma Non•insulin dependent diabetes Ulcerative colitis Rheumatoid arthritis

PPAR gamma agonist Insulin sensitizer

Tablet formulation Anti-inflammatory

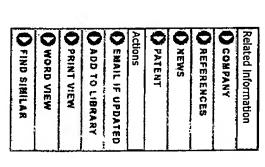
Minor editorial amendment, 1 reference added [649382]

Reason for update on 09 February 2006

gummary

trials had been initiated in rheumatoid arthritis (RA) [638027]. By February 2006, Glaxo expected phase III trials of rosiglitazone with simvastatin (qv) to begin later that year [649382]. to enter phase II trials in Alzheimer's disease later that year [649382]. In July 2005, a phase II trial was trials were ongoing [638027]; by February 2006, the company expected an extended-release formulation initiated in asthma patients, due to be completed by March 2008 [632116]. In November 2005, phase II asthma [515870], [632116]. It was launched in the US and Mexico for diabetes in June 1999 [327686] GlaxoSmithKline, GSK) as a treatment for non-insulin dependent diabetes mellitus (NIDDM/type II) been developed and launched in several major markets by SmithKline Beecham (SB; now Rosiglitazone (Avandia), a peroxisome proliferator-activated receptor (PPAR)-gamma receptor agonist, has 2003, the compound was in phase II trials for Aizheimer's disease (AD) [**515870**] and in November 2005 [333230], and by June 2000, had also been faunched in the UK and Germany [376124]. By December [263572]. It is also in development for several other indications, including Alzheimer's disease (AD) and

efficacy for this indication [628420], [628419] and no further development for psoriasis has been reported initiated [515870]. However, the results reported in October 2004 showed that the compound had no The compound has also previously been developed for psoriasis; in 2003, phase III trials for psoriasis were



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netoglitazone

Company

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Indications

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Actions

Drug

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SEARCH

Phase 2 Clinical Mitsubishi-Tokyo Pharmaceuticals Inc

Non-insulin dependent diabetes Metabolic disorder

Insulin sensitizer

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PPAR delta agonist PPAR alpha agonist Hypoglycemic agent PPAR gamma agonist

FIND BIMILAR

Reason for update on 12 January 2006

Minor editorial amendment

O COMPANY Related Information **REFERENCES** Actions PRINT VIEW ADD TO LIBRARY DEMAIL IF UPDATED PATENT) NEWS WORD VIEW

Summary

agonist (alpha, gamma and delta), as a potential treatment for type 2 diabetes and other metabolic diseases [204644], [423717], [594833]. By March 2004, phase II trials had been initiated in Japan [538366], [520195]; these trials were ongoing in November 2004 [595948]. In April 2005, Perlegen was planning US RWJ-241947; isaglitazone), a thiazolidinedione triple peroxisome proliferation activated receptor (PPAR) Perlegen and Mitsubishi Pharma (formerly Mitsubishi-Tokyo) are developing netoglitazone (MCC-555 clinical trials [594833].

had listed netoglitazone as being in phase II trials [304271], [322655]; however, by May 2003, the agreement between Mitsubishi and J&J had been terminated [491163]. Johnson & Johnson (J&J) was previously developing the compound outside of Japan and, in April 1999,

PRECLINICAL DATA

endothelial cells was dose-dependently inhibited by netoglitazone, suggesting beneficial effects on endothellum in early stage of atherosclerosis, mediated by PPAR alpha or PPAR delta [492285]. dependent manner in vitro. Monocyte chemotactic protein-1 (MCP-1) secretion from human aortic In June 2003, precinical data on netoglitazone were presented at the 63rd ADA meeting in New Orleans, LA Netoglitazone inhibited TNFalpha-Induced vascular cell adhesion molecule-1 (VCAM-1) expression in a dose-

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Drug Report

Company reglitəzar

SEARCH

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Drug

Actions Indications

No Development Reported Japan Tobacco Inc

Insulin sensitizer Non-insulin dependent dlabetes

PPAR gamma agonist

PPAR alpha agonist

Reason for update on 24 March 2004

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indexing updated, literature evaluation added, one or more development 5 references added [515261, 389917, 431904, 473077, 464687], status entries have been updated

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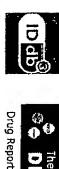
agonist, as a potential oral treatment for Type II diabetes [249397]. By 1998, reglitazar was in phase II trials in the UK for Type II diabetes [290700]; in July 2001, phase III trials were expected to commence drug candidate based on an assessment of its results [466412]. Japan Tobacco was developing **reglitazar** (JTT-501), an Insulin sensitizer and PPARalpha and gamma later that year [402336]. However, in October 2002, the company decided to terminate development of the

Pharmacia Corp (formerly Pharmacia & Upjohn) had development and marketing rights worldwide except for Japan and Korea [289901], although in April 2002, the company reported that it was no longer involved in the development of regiltazar [445305]. Phase II trials had commenced in Japan, where development reported on this collaboration since 1998 Welfide (now Mitsubishi Pharma) was codeveloping the compound [304419]; however, there has been no

following a pathway similar to that through which insulin exerts its own effect [429965]. meeting, Glasgow, UK. In vitro and in vivo studies suggested that regiltazar exerted its antidiabetic action In September 2001, preclinical data were presented at the European Association for the Study of Diabetes

demonstrated that, in the Type II db/db male mice model, EC50 values (microM) for PPARalpha and gamma agonism were (alpha/gamma): rosigiltazone (qv) 0.1/5; pioglitazone (qv) 1/7; NNC-61-0029 (qv) 0.6/3; regiitazar 0.4/2; MCC-555 (qv) 3/0.1; KRP-297 (qv) 0.5/0.4; GI-262570 (qv) 0.002/0.3; and, fenoacid In June 2001, data on regiltazar were presented at the 61st ADA meeting in Philadelphia, PA. These data

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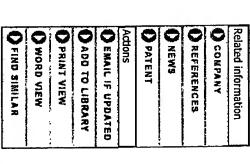
Phase 2 Clinical Unidentified

Glaxo Wellcome pic

Fibrosis Non-insulin dependent diabetes Cardiovascular disease

PPAR gamma agonist Retinoid X receptor modulator insulin sensitizer

one or more development status entries have been updated, indexing Reason for update on 02 December 2005



Summary

updated

proliferator-activated receptor (PPAR)-gamma agonist and retinoid x receptor modulator, for the potential treatment of hepatic fibrosis [638027], and investigating it for the potential treatment of cardiovascular GlaxoSmithKline (formerly Glaxo Wellcome) Is developing fargiltazar (GW-262570), a peroxisome [638027]. diseases [**470611**], [**464521**]. In November 2005, farglitazar was in phase II trials for hepatic fibrosis

of the compound for this indication had ceased as It did not meet its target profile. Alternative indications for that the field would not be obvious to people who had not studied the group of compounds very closely the compound were being explored at that time, but the company would not disclose these, only revealing [426569], [427414] The compound was previously under development for type II diabetes, for which it reached phase III trials [230289], [335170], [399771], [409231]. However, In October 2001, it was reported that development

CARDIOVASCULAR DISEASE

levels of the target genes FABP3 and aP2. Increased vasodilator NO levels (p < 0.05) and fluid retention In November 2002, predinical data on farglitazar were presented at the AHA meeting in Chicago, IL. Rats receiving 8 mg/kg bid po farglitazar showed PPAR-gamma activation through detection of increased mRNA were observed, while the glomerular filtration rate, effective renal plasma flow and renal filtration fraction





Drug Report

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Company

YM-440

Drug SEARCH

Indications

Highest Dev Status

Astellas Pharma Europe BV

COMPANY Related information

No Development Reported Non-insulin dependent diabetes

Hypoglycemic agent Insulin sensitizer

Reason for update on 24 March 2004

development status entries have been updated status entries have been updated, indexing updated, one or more 1 reference added [390055], indexing updated, one or more development

PRINT VIEW BEHAIL IF UPDATED Actions ADD TO LIBRARY NEWS REFERENCES FIND SIMILAR WORD VIEW

Summary

development has been reported since. By May 2002, **YM-178** (qv), a beta 3 receptor agonist, appeared to have superceded **YM-440** in Europe for this Indication. the compound has not appeared on a company pipeline since May 2000 [365756], and no further Insulin-dependent diabetes. The company had begun phase II trials in Europe by 1999 [326891]; however Yamanouchi Europe was developing YM-440, an insulin sensitizer, for the potential treatment for non

different mechanism of action to the thiazolidinediones as a class. Specifically, YM-440 showed only weak male mice. Although similar in some respects to troglitazone (qv), Yamanouchi claims that YM-440 has a activity against PPAR-gamma [279360]. An oral dose of YM-440 30 mg/kg od, for four days caused a reduction of 39% in blood glucose levels in

Administration of 100 mg/kg, YM-440 to diabetic db/db mice for two weeks significantly decreased blood glucose concentrations (418 to 243 mg/dl); notably, there was no significant increase in body weight gain at PPAR-gamma activity [293702]. the end of the treatment (in contrast to troglitazone and ploglitazone, (qv)). YM-440 did not affect

YM-440 is (Z)-1,4-bis-4-[(3,5-dioxo-1,2,4-oxadiazolidin-2-yl-methyl)]phenoxybut-2-ene [293702].

In February 1999, Lehman Brothers predicted the first major product launch to be in 2002, with sales

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KRP-297

Highest Dev Status Company

Drug

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Technologies

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Kyorin Pharmaceutical Co Ltd Discontinued

Non-insulin dependent diabetes Hyperlipidemia

Antihyperlipidemic agent PPAR alpha agonist PPAR gamma agonist nsulin sensitizer

Tablet formulation

1 reference added [620284]

Reason for update on 30 August 2005

Related information O COMPANY REFERENCES DEMAIL IF UPDATED O PATENT ADD TO LIBRARY Actions C NEWS WORD VIEW FIND BIMILAR DAINT VIEW

Summary

in November 2003 for safety reasons [**514245**]. In December 2003, Kyorin announced that it was also discontinuing the development of **KRP-297** [**520055**]. a PPAR alpha and gamma agonist, for the potential treatment of diabetes and hyperlipidemia [311944], Merck & Co subsidiary Banyu, in collaboration with Kyorin, was developing KRP-297 (MK-767, L-410198), [516815]. Merck had initiated phase III trials in December 2002 [473816], but discontinued development [506609]. By September 2002, the companies were conducting phase II trials in Japan [488534],

2003, the company discontinued its phase III development program because a long-term safety assessment program had identified a rare form of malignant tumors in mice [514245]. At this time, Kyorin was in discussion with Merck on the future development of KRP-297 in Japan [518196]. As of December 2002, Merck had been developing **KRP-297** as MK-767 [**473816**]; however, in November

CLINICAL STUDIES

doses from 1 to 80 mg were well tolerated. Plasma AUC and Cmax values increased with dose and the terminal half-life of **KRP-297** was 36 h. A standard breakfast did not affect the absorption of a 5 mg oral Meeting on PPARs in Fiorence, Italy. A double-blind, randomized, placebo-controlled, single-dose trial was In March 2003, clinical data on KRP-297 were presented at the Lorenzini Foundation's Second International performed to determine the safety, tolerability, pharmacokinetics and lipid effects of KRP-297. Single oral

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Indications

No Development Reported

Eli Lilly & Co

Diabetic complication Insulin sensitizer

NEWS

REFERENCES O COMPANY Related Information

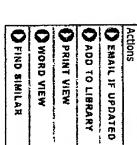
PPAR gamma agonist

Reason for update on 05 November 2002

Ddb Portal

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Indexing updated



Summary

TA-174 is a thiazolinedione peroxisome proliferator-activated receptor (PPAR) gamma agonist which was under investigation by Eli Uily in collaboration with Tanabe as a hypoglycemic agent for the potential problems [155124] and although Tanabe continued to investigate the compound, no development has been treatment of diabetic complications. Lilly discontinued development of the drug in 1993 due to toxicity reported by the company since 1997 [367139].

Development Status

Detailed status for Eli Lilly & Co

Diabetic complication Indication S Country

Status Discontinued

Detailed status for Tanabe Seiyaku Co Ltd

Country

Diabetic complication

Indication

Japan Status No Development Reported

155124 Reference

Date 01 September 1993

NISTORY

Reference Date

18 May 2000

2006/03/06

Chemistry

Structure

1/6 ペーツ





Drug Report

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Company

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NC-2100

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Indications

Nippon Chemiphar Co Ltd

COMPANY

REFERENCES

Related information

Non-insulin dependent diabetes

NEWS

PPAR gamma agonist Insulin sensitizer

Reason for update on 08 May 2003

1 reference added [488447]

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Summary

such as pioglitazone (qv) and troglitazone (qv) [371071]. glucose and triglyceride concentrations to levels comparable to those achieved with PPAR-gamma activators the potential treatment of diabetes. In KKAy obese mice NC-2100, 0.1% for two weeks, lowered plasma NC-2100 Is a thiazolidinedione PPAR-gamma activator which is under investigation by Nippon Chemiphar for

Development Status

Detailed status for Nippon Chemiphar Co Ltd

Indication

Non-insulin dependent diabetes

Japan Country

Status

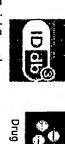
Discovery

371071 Reference

Date 16 June 2000

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Drug Report

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muraglitazar

Company

Bristol-Myers Squibb Co

Related information

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Technologies

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Reason for update on 22 December 2005

added [642539]

Highest Dev Status Indications

Pre-registration Non-Insulin dependent diabetes Metabolic disorder

Antihyperlipidemic agent PPAR alpha agonist Hypoglycemic agent PPAR gamma agonist Insulin sensitizer

Oral formulation

Summary

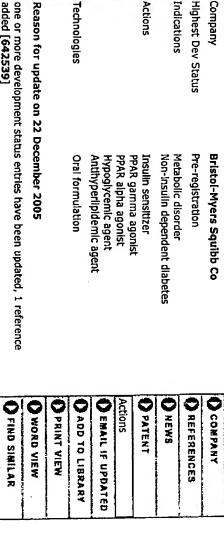
expected to take 5 years. At that time, BMS Intended to meet with the FDA to discuss its options, including discontinuing development [630997]. By December 2005, discussions with the FDA were ongoing that month, BMS announced its would have to complete additional trials to secure approval. These were An NDA was submitted in December 2004 [577532]. In October 2005, the FDA Issued an approvable letter PPAR alpha/gamma agonist, as a potential oral treatment for type 2 diabetes and other metabolic disorders. requesting additional information to support the cardiovascular safety profile of the drug [629049]. Later Bristol-Myers Squibb (BMS) is developing muraglitazar (BMS-298585; Pargluva; structure shown), a dual 642539]

Merck & Co was codeveloping the drug with BMS. However on receipt of the FDA approvable letter in October 2005, the companies began discussions to terminate the collaboration [630997]. In December 2005, BMS and Merck reached an agreement for the return of the drug to BMS [**642539**].

By March 2003, backup compounds (qv) were also under Investigation [486672]

REGULATORY INFORMATION

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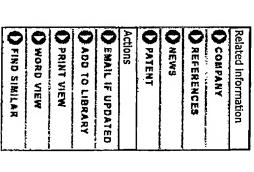
Phase 3 Clinical AstraZeneca pic

Heart arrhythmia Non-insulin dependent diabetes Insulin dependent diabetes ⊔pld metabolism disorder

Antihyperlipidemic agent Antiarrhythmic agent PPAR alpha agonist Hypoglycemic agent PPAR gamma agonist

Reason for update on 10 February 2006 Oral formulation

1 reference added [648528], Minor editorial amendment



Summary

a worldwide regulatory authority review of the safety and toxicology of PPAR agonists [563036]. In an oral dual PPAR alpha/gamma agonist, for the potential improvement of dyslipidemia and glycemic control of 2007 was dependent upon the results of ongoing phase III studies and discussions with the FDA track for a 2007 submission [624516]; in February 2006, the expected submission date of the second half In type 2 diabetics [275466], [377656]. In October 2003, phase III trials were being initiated [507400], AstraZeneca (formerly Astra) is developing tesaglitazar (AZ-242, AR-H039242, Galida; structure shown), November 2005, phase Π trials were underway in Japan [$oldsymbol{638194}$]. By September 2005, tesaglitazar was on 2006 to 2007 as a result of AstraZeneca agreeing to extend long-term follow-up studies to 2 years following [507401]; these were ongoing In October 2004. At that time, the anticipated filing date was moved from [648480], [648528].

listed on the company's pipeline [402040]. In December 1999, the compound was also being developed as a potential antiamhythmic drug [349551], [314472], [377656]; as of March 2001, however, diabetes and insulin resistance were the only indications

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Drug Report

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Dr Reddys Research Foundation

Discontinued

Non-insulin dependent dlabetes Hyperlipidemia Insulin sensitizer

PPAR gamma agonist Hypoglycemic agent Antihyperlipidemic agent PPAR alpha agonist

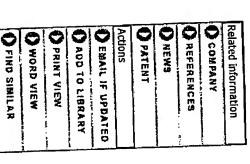
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Reason for update on 05 May 2004

Minor editorial amendment, one or more development status entries have been updated, literature evaluation added, indexing updated



Summary

alpha and gamma agonist that regulates blood glucose and lipid levels, was being developed by Novo treatment of non-insulin dependent (Type II) diabetes [325344], [416231]. In November 2001, phase III Nordisk (previously in collaboration with Novartis), under license from Dr Reddy, for the potential Ragaglitazar (NN-622, (-)DRF-2725; structure shown), a PPAR (peroxisome proliferator-activated receptor) trials were ongoing but Novo Nordisk revealed that it was planning to outlicense the compound [443186] trials were initiated both in the US and in Europe [428278], [440091]. In February 2002, these phase III time, the company planned to continue all other activities in the development program until it completed a renewed benefit/risk assessment of **ragaglitazar**, the results of which would be ready by the first quarter of the formation of bladder tumors in one mouse and a number of rats after treatment with the drug. At this postponed all planned future trials. This decision was made in response to preclinical studies that revealed [438928]. In July 2002, Novo Nordisk decided to suspend all current clinical trials of ragaglitazar and [478217], [478168] However, by February 2003, **Novo Nordisk** had decided not to pursue further development of the program 2003. Filing for approval was expected to be delayed by two years [458773], [458774], [460379].

CLINICAL INFORMATION

Worldwide phase II trials had begun by September 2000 [381826], [385666]. By July 2001, Novo Nordisk expected to complete phase II trials later in that year [416231]; and, by September 2001, the

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